

ATTORNEY DOCKET NO. 011927-113100
Application No. 10/004,413

REMARKS

I. Status of the claims

Claims 22-35 are pending in this application.

II. Rejections under 35 U.S.C. § 103(a)

The Examiner has rejected claims 22-27 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 3,988,358 ("Heck") in view of U.S. Patent No. 5,296,601 ("Suto"), and claims 28-35 under 35 U.S.C. § 103(a) as being unpatentable over Heck in view of U.S. Patent No. 4,704,467 ("Wehrenberg") and Suto.

In both rejections, the Examiner references Heck as teaching a process of producing carboxylic acid esters by reacting aryl, heterocyclic, or benzylic halides with various substituted derivates, including a nitro, allyl, or substituted halogen groups, with carbon monoxide and an alcohol in the presence of a palladium catalyst and a tertiary amine. The Examiner states that Heck differs from Applicants' invention in that the metal catalyst used by Heck is a heterogeneous catalyst of palladium metal deposited on activated carbon. Heck teaches the use of a palladium complex, PdL_n, as the catalyst. The reaction scheme of Heck involves ligand (L) displacement from the Pd complex as an initial step in its process. See Heck, col. 1, lines 36-53. The claimed invention, as the Examiner has recognized, recites a heterogeneous catalyst of palladium metal on carbon and does not employ a palladium complex as the catalyst.

To cure the deficiencies of Heck, the Examiner cites Suto. According to the Examiner, Suto expressly teaches the application of either the homogeneous catalyst containing palladium or the heterogeneous catalyst, such as palladium carbon, to the process. In Suto, the Examiner finds an equivalency between the use of the homogeneous catalyst and that of the heterogeneous catalyst on processes of producing carboxylic acid esters.

Applicants respectfully disagree with the Examiner's interpretation of Suto as teaching a heterogeneous catalyst. On page 6, lines 13-26, Applicants explain the difference between homogeneous catalysts and heterogeneous catalysts. Homogeneous catalysts are catalysts that have complexed with donor ligands, such as phosphines; heterogeneous catalysts are catalysts wherein the metal can be used alone or supported on an inert matrix, such as activated carbon. See Specification, page 6, lines 13-26. As discussed below, Suto, like Heck, only teaches homogeneous catalysts and does not teach heterogeneous catalysts.

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When discussing the use of a catalyst for the process of producing carboxylic acid esters, Suto states that the catalyst should contain both a palladium compound and a phosphine compound. When discussing the palladium compound, Suto states:

The palladium compound as catalyst in this invention is used in combination with a phosphine compound. The palladium compound include, for example, metallic palladium, palladium carbon, palladium alumina, palladium chloride, palladium bromide, palladium acetate, dichlorobiscyanophenylpalladium, dichlorobistriphenylphosphine palladium, tetrakis(triphenylphosphine) palladium, etc.

Col. 4, lines 61-69 (emphasis added). After this passage, Suto discusses phosphine compounds that can be used *in combination* with the palladium compound. See col. 5, lines 1-20. In both discussions, Suto states that palladium compound and phosphine compound are used in combination with each other. Furthermore, all 21 examples of Suto use a combination of a palladium compound with a phosphine compound. No examples use a catalyst that is not a combination of a palladium compound and a phosphine compound. For comparison, see Applicants' Example 3, exemplifying a reaction using a heterogeneous catalyst. Suto, therefore, does not contemplate using a palladium compound by itself or as a heterogeneous catalyst.

The Examiner references palladium carbon as an example of Suto teaching a heterogeneous catalyst. Suto, however, only discloses palladium carbon as a possible palladium compound that is combined with the phosphine compound to form the catalyst. Suto does not teach the use of palladium carbon by itself as a catalyst. Since Suto only teaches a catalyst combining a palladium compound with a phosphine compound, Suto only teaches a homogeneous compound; heterogeneous catalysts are not disclosed in Suto.

Wehrenberg also fails to cure the deficiencies of Heck and Suto. The Examiner cites Wehrenberg as teaching a method of preparing mercaptobenzoates by reacting a nitro-substituted aromatic carboxylic acid ester which has mercaptan in the presence of an inorganic base, non-polar aprotic solvents and a phase-transfer catalyst. As the Examiner points out, however, Wehrenberg does not disclose the following elements of Applicants' claimed process: the intermediate reactions, carbon monoxide, alcohol, proton acceptor, and a heterogeneous catalyst of palladium metal deposited on activated carbon. Because Wehrenberg does not teach heterogeneous catalysts, Wehrenberg fails to cure the deficiencies of Heck and Suto.

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When rejecting claims 22-27, the Examiner relies on Suto for teaching the equivalency between the use of a homogeneous and heterogeneous catalyst in a process for producing carboxylic acid esters. The Examiner also relies on Suto for this same teaching when rejecting claims 28-35. Since the Examiner has relied on Suto for all the § 103 rejections, and since Suto does not teach an equivalence of homogeneous and heterogeneous catalysts (or even heterogeneous catalysts at all), the § 103 rejections must fall. Accordingly, Applicants respectfully request that the Examiner withdraw these § 103 rejections.

III. Rejections under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 22, 29, 31 and 35 under 35 U.S.C. § 112, first paragraph. The Examiner finds that the specification fails to provide reasonable enablement with regard to the following claim terms: nitro-substituted aromatic carboxylic ester with any heteroaryl containing at least one heteroatom of N, O, or S; tertiary amine base; and phase-transfer catalyst. Applicants discuss each of these rejections below.

Nitro-substituted aromatic carboxylic acid ester: The Examiner starts this rejection by stating that Applicants' specification is enabling for nitro-aromatic carboxylic acid esters containing various aryl groups, such as phenyl, furyl, benzofuranyl, pyranlyl, thienyl, pyrrolyl, etc. Applicants, on page 4 of the specification, have provided other aryl groups that may be used with the nitro-aromatic carboxylic acid esters of the invention. See page 4, last paragraph. The compounds illustrated in the Examiner's list represent various substituted and unsubstituted aromatic compounds. Substituted aromatic compounds include those substituted by oxygen (furyl, benzofuranyl), nitrogen (pyranlyl, pyrrolyl), and sulfur (thienyl). The Examiner next states that the specification does not enable the nitro-substituted aromatic carboxylic esters with any heteroaryl containing at least one heteroatom N, O, S.

But the Examiner provides no reasoning why one skilled in the art would not be able to produce nitro-substituted aromatic carboxylic acid esters similar in size and function to those stipulated to by the Examiner as enabled. Specifically, the Examiner has provided no evidence why one skilled in the art would not be able to produce an aromatic carboxylic acid ester wherein the aryl group is a heteroaryl containing one or more oxygen groups when the Examiner has stipulated that two such compounds (furyl and benzofuranyl) are enabled; the Examiner has

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provided no evidence why one skilled in the art would not be able to produce an aromatic carboxylic acid ester wherein the aryl group is a heteroaryl containing one or more nitrogen groups when the Examiner has stipulated that two such compounds (pyranyl and pyrrolyl) are enabled; and the Examiner has provided no evidence why one skilled in the art would not be able to produce an aromatic carboxylic acid ester wherein the aryl group is a heteroaryl containing one or more sulfur groups when the Examiner has stipulated that heteroaryl sulfur compounds, such as thienyl, are enabled. By the Examiner's own stipulation, aromatic carboxylic acid esters wherein the aryl group is a heteroaryl containing nitrogen, oxygen or sulfur are all enabled.

If one skilled in the art is able to prepare nitro-substituted aromatic carboxylic acid esters from nitro-substituted aryl halides wherein the aryl group of the nitro-substituted aryl halide is a heteroaryl group such as furyl, benzofuranyl, pyranyl, thienyl, pyrrolyl, one skilled in the art surely would also be able to prepare similar esters when the aryl group comprises other groups that similarly contain at least one heteroatom of N, O or S. There is no evidence that heteroaryl groups other than furyl, benzofuranyl, pyranyl, thienyl, pyrrolyl would react differently in Applicants' process than furyl, benzofuranyl, pyranyl, thienyl, pyrrolyl. As the compounds would be similar in both size and functionality, a high degree of predictability exists for compounds of this nature, especially when such compounds are being used in the same reaction scheme, in this case, Applicants' claimed process.

It would not take a skilled artisan undue experimentation to make nitro-substituted aryl halides wherein the aryl group is a heteroaryl containing at least one heteroatom of N, O or S. This is especially true given the various heteroaryl compounds containing at least one heteroatom of N, O or S that the Examiner has stipulated to as being enabled by the specification.

Moreover, using various substituted and unsubstituted aryl halides for reactions forming aromatic carboxylic acid esters is customary in the art. Heck and Suto, two references cited by the Examiner, both provide exhaustive lists of substituted and unsubstituted aryl halides that may be used in processes for producing carboxylic acid esters. See Heck, col. 2, lines 3-15 and Suto, col. 3, lines 35-37 and col. 3, line 48 to col. 4, line 32. As shown in these references, the art recognizes that processes for preparing carboxylic acid esters may utilize various substituted and unsubstituted aryl halides, suggesting the interchangeability among the groups. Indeed, the

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degree of predictability for using the various substituted and unsubstituted aryl halides in these types of reactions appears quite high.

Accordingly, Applicants respectfully request that the Examiner withdraw this § 112 rejection.

Tertiary-amine base: The Examiner states that while the specification provides enablement for particular tertiary amine bases, such as triethylamine and tri-n-butylamine, the specification does not reasonably provide enablement for all tertiary amines. See page 7, lines 14-19. Applicants use the tertiary amine bases in this invention as proton acceptors to assist the reaction of a nitro-substituted aryl halide with carbon monoxide and an alcohol to form a corresponding nitro-substituted aromatic carboxylic acid ester. As set forth in the specification, the proton acceptor may be any suitable proton acceptor known in the art that acts as such; i.e., a Brønsted-Lowry base. See page 7, lines 14-19. Applicants have specified tertiary amine bases as the preferred proton acceptors, but the reasoning behind using a tertiary amine base in this reaction remains the same: to provide the reaction with a satisfactory proton acceptor.

It is well known in the art that tertiary amine bases act as good proton acceptors. One skilled in the art, when selecting a tertiary amine for use as a proton acceptor, would have sufficient guidance from the disclosure of the application for this selection process. In fact, it would be difficult for one skilled in the art to select a tertiary amine base that did not act as a proton acceptor. Certainly it would not take one skilled in the art undue experimentation to determine which tertiary amine bases act as acceptable proton acceptors when preparing nitro-substituted aromatic carboxylic acid esters from nitro-substituted aryl halides. Even Heck, a prior art document cited by the Examiner in this Office Action, discloses the use of basic tertiary amines as proton acceptors, citing nine basic tertiary amines as examples. See Heck, col. 1, lines 52 (last reaction) and col. 2, lines 43-54. Clearly, suitable tertiary amines and their use as proton acceptors are well known to those of skill in the art.

It would not take one skilled in the art undue experimentation to determine from the specification suitable tertiary amine bases that may be used in Applicants' claimed invention. Accordingly, Applicants respectfully request that the Examiner withdraw this enablement rejection with regard to the tertiary-amine bases.

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Phase-transfer catalyst: The Examiner states that while the specification enables certain phase-transfer catalysts, such as tetrabutylammonium bromide and tetrabutylammonium chloride, the specification does not provide reasonable enablement for all phase-transfer catalysts. As set forth in the specification, conversion of the nitro-substituted aromatic carboxylic acid ester to the thioester-substituted aromatic carboxylic acid ester may be performed by any means that promotes displacement of the nitro group with a thioether group. Preferably, the conversion is conducted in a homogeneous solvent system or a phase-transfer solvent system that contains a phase-transfer catalyst in a water-immiscible solvent and optionally water. The phase-transfer catalyst may be chosen from readily available ammonium or phosphonium salts. See page 9, line 21 to page 10, line 7.

It is well known in the art that phase-transfer catalysts may be used in phase-transfer systems to promote certain substitution reactions, such as the substitution reaction involved in displacing the nitro group in favor of the thioester group illustrated in Scheme B. See specification, page 9. The art recognizes the use of phase-transfer catalysts for this purpose. Wehrenberg, a reference cited by the Examiner, discloses and claims the term "phase-transfer catalyst" to describe the catalyst that promotes the displacement of the nitro group in the reaction. See also, Wehrenberg, col. 2, lines 14-17 and claim 1. Wehrenberg refers to this catalyst by the same name as that used by Applicants and uses the catalyst for the same function as that disclosed in Applicants' specification.

As suitable phase-transfer catalysts are well known to those of skill in the art, one skilled in the art would have ample guidance from the specification in selecting a suitable phase-transfer catalyst to use for this reaction. Certainly, it would not take undue experimentation for one skilled in the art to select a suitable phase-transfer catalyst that would successfully promote the reaction as described.

The Examiner notes that catalyst compositions represent an unpredictable aspect in the art of organic chemistry. The phase-transfer catalysts being used in this invention, however, are not being utilized in a new manner. Rather, well-known catalyst systems are being used in known methods. The use of the phase-transfer catalyst in the manner described in this invention does not, therefore, require undue experimentation. The disclosure, as filed, is fully enabling for the claimed invention and the term "phase-transfer catalyst."

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It would not take one skilled in the art undue experimentation to determine from the specification suitable phase-transfer catalysts that may be used in Applicants' claimed invention. Accordingly, Applicants respectfully request that the Examiner withdraw the enablement rejection with regard to the phase-transfer catalyst.

IV. Rejections under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 24, 25, 30, 31 and 33 under 35 U.S.C. § 112, second paragraph. The Examiner has objected to the phrases, "aliphatic hydrocarbon," "aromatic hydrocarbon," "acyclic ether," "polar aprotic solvent," "water-miscible solvent," and "water-immiscible organic solvent." Applicants respectfully traverse this rejection.

Each of the terms listed by the Examiner have well-known definitions in the context of the art for which they are being applied. One skilled in the art would know which group of compounds is encompassed by them. As the terms are not vague or indefinite to one skilled in the art, the skilled artisan would not be confused as to which hydrocarbons, ethers or solvents Applicants are referring to when using the terms. The specification provides additional guidance as to acceptable examples of compounds falling within each of the terms. See page 9, line 21 to page 10, line 7. One of ordinary skill would readily comprehend these terms and understand the metes and bounds of Applicants' claimed invention with regard to the terms. Accordingly, Applicants request that the Examiner withdraw these § 112, second paragraph rejections.

The Examiner has also objected to the term "C₄-C₁₀ aryl or heteroaryl group," both in its recitation in the claims and its disclosure in the specification. The Examiner objects to this term on the belief that an aryl group must contain six or more carbons.

While many aryl groups do contain six carbons, such as phenyl, aromaticity is not limited to only those compounds having six or more carbon atoms. Indeed, six-membered rings containing one or more non-carbon atoms may nonetheless have aromatic properties even though less than six carbon atoms are present in the ring. Pyrazine is an example of a six-membered aromatic ring containing four carbon atoms and two nitrogen atoms. Pyrazine would be thus be considered a C₄ heteroaryl group, and fall within Applicants definition of a C₄-C₁₀ aryl or heteroaryl group. The term "C₄-C₁₀ aryl or heteroaryl group" therefore appropriately describes Applicants' desired group of compounds, and would be recognized as so by those of skill in the art.

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As the meaning of this term is well understood by those in the art, it would not be considered vague or indefinite. Its disclosure in the specification and recitation in the claims is thus appropriate. Accordingly, Applicants respectfully request that the Examiner withdraw the objections to this term.

V. Objection to the specification

The Examiner has objected to the term "C₄-C₁₀ aryl or heteroaryl group" in the specification. Applicants discuss this objection in the preceding paragraph and respectfully request that the objection be withdrawn.

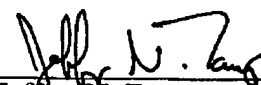
VI. Conclusion

Applicants respectfully request reconsideration of this application in view of the above remarks.

Except for issue fees payable under 37 C.F.R. §1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account No. 19-2380. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. §1.136(a)(3).

Respectfully submitted,

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